REMARKS/ARGUMENTS

Claims 4-6, 10, 15, 19, 32, 39, 40, 45, 49 and 52-64 are pending in this application. Of those pending, claims 4-6, 10, 15, 19, 32, 39, 40, 45, 49, 52, 53 and 58-64 are withdrawn from consideration by the Examiner as being directed to a non-elected invention. Claims 54-57 are under examination and have been rejected.

In this response, the text on pp. 77-78 of applicants' specification has been amended, i.e., in order to correct a typographical error in the legends for Figs. 15 to 18. The EPO doses indicated as being "0.1 mg Aranesp per kg" has been corrected to read as "0.1 μg Aranesp per kg". Support for this amendment is found at p. 75, first and second paragraphs, and p. 83, first paragraph, of the application as filed.

In addition to the specification amendments discussed above, claim 54 has been amended to more clearly recite applicants' claimed method. Support for the claim amendments is set forth, *inter alia*, at pp. 38-40 and pp. 44-45, as well as in original claim 9 and claims 55-56 added in applicants' response dated April 29, 2009 whereupon original "Use" claim 1 was re-written as method claims 54-57. Claims 55 and 56, furthermore, are canceled from the application in this response without prejudice or disclaimer because the subject matter of those claims is now introduced by amendment into claim 54.

No new matter is added by the amendments made either to the specification or the claims and, thus, entry of these amendments is respectfully requested. Upon such entry, claims 4-6, 10, 15, 19, 32, 39-40, 45, 49, 52-54 and 57-64, as amended, will be pending in the application with claims 54 and 57 being under examination. Reconsideration of the application is respectfully requested.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 54-57 are rejected on pp. 3-4 of the Office Action under 35 U.S.C. §112, second paragraph. The Office Action states in regard to the rejection that the claims are indefinite because it is not clear what is actually is being treated and/or what is being exhibited in the human/animal subject. Additionally, the Office Action goes on to state that the claims should recite the goal that must be achieved, i.e., with a step that clearly relates back to the preamble.

In response, claim 54 is amended as indicated above. The amendments to the claim are believed to overcome the grounds for rejection under 112, second paragraph.

The Examiner is respectfully requested to reconsider and withdraw the rejection.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

a) the "written description" rejection

Claims 54-57 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement of the statute. The Examiner argues that the written description of applicants' invention does not describe diseases or conditions which display at least one dysfunction of endothelial progenitor cells AND at least one cardiovascular risk AND at least one-end organ damage. The Office Action states (p. 5) further that the specification as filed does not provide a written description or set forth the metes and bounds of these "limitations".

Thus according to the Office Action, "The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed." The Examiner alleges that the above rejection is a "new matter" rejection and states that applicant must either cancel the alleged new matter, or alternatively, demonstrate specific written support for the "limitations", or else rely on the limitations set forth in the specification as filed.

In response, applicants have substantially modified claim 54 such that the amended claim is believed to properly set forth the "metes and bounds" of applicants' method along the lines described in the specification as filed. As now amended claim 54 states, *inter alia* that applicants' method is directed to a method for treating acute or chronic renal failure in a human or animal patient wherein such patient exhibits a) at least one dysfunction of endothelial progenitor cells, b) at least one cardiovascular risk factor, wherein the factor is selected from the group consisting of hypertension, hypercholesterolemia, elevated asymmetric dimethylarginine (ADMA) levels, increased insulin resistance and hyperhomocysteinemia, and c) at least one end-organ damage, wherein the at least one end-organ damage is selected from the group consisting of left ventricular hypertrophy, microalbuminuria, cognitive dysfunction, increased thickness of the intemia media in the carotid artery, proteinuria and a glomerular filtration rate of 30 to 80

ml/min. The method comprises administering to the patient a pharmaceutical composition comprising a subpolycythemic dosage of 1 to 90 IU EPO/kg of body weight per week of at least one of erythropoietin and derivatives thereof, wherein the acute or chronic renal failure is thereby treated in the human or animal patient.

The method as now recited in amended claim no. 54 is thus directed to a clearly defined patient group, i.e., those suffering from acute or chronic renal failure which are in addition specifically characterized by a) at least one dysfunction of endothelial progenitor cells, b) the presence of a cardiovascular risk factor, and c) the presence of end-organ damage, in particular a glomerular filtration rate of 30 to 80 ml/min. As would, furthermore, be well understood by those working in this field, such very specific patients have kidneys which are still able to filtrate, but which are beginning to suffer the effects of renal insufficiency. Thus these patients already exhibit end-organ damage which, however, has not yet resulted in a complete terminal renal insufficiency, such as a complete renal failure.

The Examiner's attention is respectfully directed to Examples 3 and 4 (see, e.g., pp. 82-84) and the corresponding figures provided in the present application. Applicants submit that the subject examples clearly demonstrate that in animal patients, namely the rats used in the examples, the above-noted symptoms, i.e., a), b) and c) are beneficially treated in accordance with the practice of the method as recited in, for example, claim 54. Applicants refer, for instance, to figures 11 to 14 which show the histological changes in Sprague-Dawley rats exhibiting chronic renal failure associated with severe end-organ damage causing a reduced glomerular filtration rate, as well as hypertension. In correlation with figure 6 indicating that rats with restricted renal function exhibit a distinct endothelial progenitor cells (EPC) dysfunction, those rats represent the specific patient group defined for treatment with the presently claimed method, i.e., having the symptoms a), b) and c) as described above (and as recited in claim 54).

As is evident from Figs. 15-18 provided with the application, the rats have been treated with 0.1 µg Aranesp/kg per week. Aranesp is a well-known EPO derivative and 0.1 µg of Aranesp corresponds to 20 IU EPO. Accordingly, the structural damage found in the control subjects that are the bases of figures 11-14 was successfully treated and reversed.

It is, thus believed by applicants to be perfectly clear from the teachings provided in the disclosure as originally filed that the treatment of a specific group of rats suffering from acute of

chronic renal failure which in addition have at least one cardiovascular risk, a dysfunction of EPC and end-organ damage is successfully achieved by treatment of low dose EPO or a derivative (such as Aranesp) with no deleterious side effects to the patient population.

For the reasons presented above, therefore, applicants respectfully submit that claim 54 as amended (and dependent claims 57) are believed to completely fulfill the requirements of the written description portion of 35 U.S.C. 112, first paragraph. The Examiner is, thus, requested to reconsider and withdraw the written description rejection of applicants' claims 54 and 57 (note: claims 55 and 56 are canceled without prejudice or disclaimer).

b) the "enablement" rejection

Claims 54-57 are rejected at pp. 6-9 of the Office Action under 35 U.S.C. §112, first paragraph, due to an alleged failure to comply with the enablement requirement of the statute. The Examiner alleges that the claims are not enabled because:

1. the claims (i.e., as set forth in the April 29, 2009 response) encompass treating any disease in a subject who exhibits at least one of a) a dysfunction of endothelial progenitor cells, b) at least one cardiovascular risk, and c) at least one end-organ damage, by administration of EPO or a derivative thereof, whereas the instant examples as provided in the application as filed only employ a renal disease population;

2. the specification fails to teach wherein a patient exhibits at least one cardiovascular risk in addition to one dysfunction of endothelial progenitor cells and at least one end-organ damage; and

3. the claims encompass derivatives of EPO but the specification does not teach how to make any derivative of the exemplified EPO polypeptide and thus the specification does not support claims to EPO polypeptides modified to an unlimited extent relative to those exemplified.

The enablement rejection of applicants' claims under 35 U.S.C. 112 is respectfully traversed.

Briefly summarizing applicants' position *viz* the three grounds cited above (i.e., a more detailed discussion of these issues is provided following this summary) applicants submit, first, that claim 54 as now amended is no longer directed to a method for treating any disease

exhibiting a), b) and/or c) above. Rather, the claim is now directed to the treatment of a specific condition, i.e., acute or chronic renal failure, wherein it is the chronic or acute renal failure that is treated and which is present in patients exhibiting conditions a), b) and c).

Secondly, as discussed above in the portion of this response dealing with the "written description" rejection under 35 U.S.C. 112, which remarks are specifically incorporated by reference into this discussion as well, applicants submit that the specification contains sufficient disclosure regarding a patient population afflicted with acute or chronic renal failure that exhibits each of the three conditions a), b) and c) associated with the acute or chronic renal failure.

Finally, the disclosure contained in the as-filed specification (i.e., concerning the Aranesp composition described in, e.g., the Examples which is, itself, an EPO derivative), taken together with the general level of knowledge of one having an ordinary level of skill in the relevant art, is believed to adequately enable the recitation of 'derivative' in applicants' claims.

The subject matter of "main" claim 54 (as presently amended) is directed to a clearly defined patient group, those suffering from acute or chronic renal failure which in addition are characterized by a) at least one dysfunction of endothelial progenitor cells, b) the presence of at least one cardiovascular risk factor, and c) and the presence of end-organ damage - in particular a glomerular filtration rate of 30 to 80 ml/min that, until the discovery of the presently claimed method, were not considered by the prior art to be susceptible to treatment with EPO. Those constituting this specifically defined patient group are characterized by a) at least one dysfunction of endothelial progenitor cells, b) the presence of at least one cardiovascular risk factor, and c) and the presence of end-organ damage - in particular a glomerular filtration rate of 30 to 80 ml/min. The specific patients that are the object of the claimed invention thus have kidneys which are still able to filtrate, but which are beginning to suffer from renal insufficiency. They are, thus, patients that are already demonstrating end-organ damage which, however, has not yet resulted in a complete terminal renal insufficiency, i.e., such as renal failure.

In the prior art, the early stage of kidney insufficiency has typically been treated with anti-inflammatory pharmaceutical compositions, such as cortisol. Additionally, such a patient's blood pressure is controlled and, if necessary, treated with a anti-hypertensive compound. Prior to the present invention, no alternatives to the above-described treatments were known.

In contrast, the treatment of terminal renal failure typically comprises the attempt to replace the function of the non-functioning kidney, either by external dialysis or else by transplantation. Furthermore, any therapy for such terminal renal failure must include the administration of high dose EPO to prevent or at least diminish the symptoms of anemia.

In sum, therefore, whereas EPO administration is known for treatments of condition(s) involving terminal renal failure, in cases of early stage renal failure, i.e., wherein terminal renal insufficiency (e.g., total renal failure) is not in issue, treatment of the patient's condition has not (in the prior art) involved the administration of EPO.

In considering, therefore, actual/potential modes of treatment, one must clearly distinguish between patients with beginning (i.e., early stage) renal failure in contrast to patients suffering from terminal (i.e., complete) renal failure in that these groups of patients are distinguishable one from the other with regard to the amount of EPO involved in the treatment. That is, as indicated above a main component involved in the treatment of patients suffering from complete terminal kidney failure is, in addition to compensating for the complete lack of kidney function *per se*, the replacement of an insufficient amount of endogenously produced EPO, whereas EPO administration in patients with early stage renal insufficiency, i.e., who are still able to endogenously produce EPO in sufficient amounts, is not considered to be necessary.

As previously noted in the discussion above regarding the "written description" rejection, Examples 3 and 4 of the present application (together with their corresponding figures and the explanations regarding the same) clearly demonstrate that EPO treatment has positive effects on the kidney tissue of animals exhibiting renal insufficiency whereupon the administration of EPO leads to tissue regeneration in subjects with early stage renal failure. To take this effect into account, applicants have now amended their 'main' claim no. 54 such that, as amended, the claim is directed to, "A method for treating acute or chronic renal failure in a human or animal patient . . . .". This is a far broader approach than that known from the prior art which, as indicated above, involved the administration of EPO to patients suffering from terminal renal failure in order to overcome the symptoms of anemia.

As applicants believe is established by the arguments and evidence discussed herein, the teachings provided in the present application clearly provide the necessary written description and enablement regarding a method for treating patients with cardiovascular risk factors in

combination with a dysfunction of endothelial progenitor cells in conditions involving an early stage renal insufficiency with EPO in low, i.e., subpolycythemic , dosages, i.e., as presently recited in (amended) claim 54. More particularly in this regard the Examiner's attention is respectfully once again directed to figures 11 to 14. As noted above, the subject figures demonstrate the histological changes in Sprague-Dawley rats exhibiting chronic renal failure associated with severe end-organ damage causing a reduced glomerular filtration rate and hypertension (a cardiovascular risk). Taken in combination with figure 6 indicating that patients with restricted renal function exhibit a distinct endothelial progenitor cell (EPC) dysfunction, those rats represent the specific patient group to be treated by the method of the present invention, i.e., as set forth in (amended) claim 54 - which is rats suffering from acute or chronic renal failure exhibiting the symptoms a), b) and c) as recited in claim 54.

As can be seen, moreover, from figures 15 to 18, the rats are treated with an EPO derivative, i.e., 0.1 μg Aranesp/kg per week (0.1 μg of Aranesp corresponds to 20 IU EPO). Accordingly, the structural damage found in the control subjects of figures 11 to 14 were successfully treated and reversed.

The above thus clearly demonstrates that the data presented in the application as filed is sufficient to enable the claimed method involving treatment of a specific group of patients, i.e., those suffering from acute or chronic renal failure which are exhibiting hypertensive damage and end-organ damage caused thereby.

As further evidence that the method as recited in. e.g., (amended) claim 54 is appropriately enabled, provided herewith is a journal article co-authored by Dr. Ferdinand Bahlmann, who is also one of the co-inventors of the presently claimed method and application. The article, cited as, Bahlmann, et al., "Low-Dose Therapy With the Long-Acting Erythropoietin Analogue Darbepoetin Alpha Persistently Activates Endothelial Akt and Attenuates Progressive Organ Failure", Circulation 2004 (110) pp. 1006 - 1012, bears a publication date of August 9, 2004, which is shortly after the filing (on January 23, 2004) of applicants' German priority application no. 10 2004 004 509.7, and just prior to the filing (on January 22, 2005) of the International Application No. PCT/EP2005/000618 upon which the present U.S. National Stage application is based. The article is also listed on the form attached to this response and the Examiner is respectfully requested to make it of record in the present application. A fee of

$180.00 is believed to be due in order to make the reference of record and the subject fee is included with the present response.

As may be seen, e.g., from the Abstract of the article and the Methods section (p. 1007) Sprague-Dawley rats were subjected to selective ligation of the extrarenal renal artery branches of the left renal artery to produce a partial renal infection. The rats thus displayed end-organ damage since the consequence of the ligation is vascular sclerosis, glomerulosclerosis and tubulointerstitial damage (see, e.g., the Abstract, p 1006, the "Methods" on p. 1007 and the "Results" on pp. 1007 -1008), leading to a reduced glomerular filtration rate which is between 30 and 80 ml/min. Furthermore, due to the above-described damages, microalbuminuria - involving a moderate increase in the presence of albumin (which constitutes a significant percentage of the protein found in urine) was observed in the rats' urine (see, e.g., the table on p. 1008 of Bahlmann, et al. and compare it with p. 40, lines 7-15, in the present application). Furthermore, as is also evident from page 1008, right-hand column, last paragraph of the Bahlmann et al. article, the rats developed hypertension which, of course, is classified as a cardiovascular risk.

Cardiovascular risk factors and renal end-organ damages are conventionally associated with a dysfunction of the endothelial progenitor cells (compare with figure 6 or with p. 18 of the present application). Although the Bahlmann et al. article does not explicitly state that the rats treated by the method described therein additionally suffer from a dysfunction of endothelial progenitor cells, i.e., as required in claim 54, applicants submit that this was so. Submitted together with this response in regard to this matter is an evidentiary declaration under 37 C.F.R. 1.132 of Prof. Dr. Hermann Haller which contains experimental data demonstrating that the rats which were the subjects of the treatments described in Bahlmann et al. (2004) also suffered from a dysfunction of EPC's. Thus the rats described in the Bahlmann et al. article did exhibit each of the conditions, a), b) and c) recited in (amended) claim 54.

Treatment of the subject rats with darbepoetin, i.e., as described in the article, which is an EPO derivative, in a low subpolycythemic dose (0.1 µg/kg/week of darbepoetin corresponds to 20 IU EPO/kg/week) - see p. 1007 left-hand column, second paragraph - results (as shown for instance at p. 1008 under the heading, "Renal Morphology" and in the "Discussion" portion of the article), significantly reduced the sclerosis, the glomerulosclerosis and the tubulointerstitial damages. Furthermore, as is evident in the table on p. 1008, the urinary protein content -

indicating structural and functional failures of the renal tissue - was also significantly reduced. This reduction clearly indicates that the kidney improved its function, i.e., due to the above-described treatment with darbepoetin administered in a subpolycythemic dose.

The therapeutic results described above as recited in Bahlmann et al. thus further support applicants' position that the method as taught and claimed in the present application is enabled in accordance with the requirements of 35 U.S.C. 112, first paragraph.

Further in support of applicants' position re enablement, also set forth in the accompanying declaration under 37 C.F.R. 1.132 of Prof. Dr. Hermann Haller filed with this response is data obtained in practicing the method recited in claim 54 on human patients suffering from acute or chronic renal failure and exhibiting a) a reduced number of endothelial progenitor cells which, of course, constitutes a dysfunction of endothelial progenitor cells, b) high blood pressure (i.e., a cardiovascular risk factor), and c) a reduced kidney function (at least one end-organ damage). As demonstrated in the declaration, treatment of the subject patients with low-dosage EPO, i.e., 30 or 83 IU/kg body weight per week, led to a significant increase in the number of endothelial progenitor cells which, in turn, serves to repair and regenerate damaged renal tissue (see, e.g., p. 19, first paragraph, in applicants' specification).

Applicants submit that the arguments and evidence noted above strongly supports the contention that the method as recited in (amended) claim 54 is entirely enabled per the requirements of 35 U.S.C. 112, first paragraph. Further in support of that contention, applicants now turn to the Examiner's 'third' basis (noted above) for the rejection based on an alleged lack of enablement, i.e., that the claims encompass derivatives of EPO but the specification does not teach one how to make any derivatives and thus the specification does not support claims to EPO polypeptides modified to an unlimited extent relative to those exemplified by said specification.

In response, applicants submit that the application defines, on pp. 21-22, the meaning applicants ascribe to the term "derivative". As indicated therein, 'derivatives' of EPO are substances having the same biological effects as EPO. From the comprehensive discussion provided regarding EPO derivatives in applicants' specification, it is believed to be clear that one having an ordinary level of skill in the relevant art would be well qualified to decide which material(s) are, and are not, derivatives of EPO as that term is used in regard to the presently claimed method, and, upon making such a determination, to obtain and appropriately use such

derivative(s).

In particular, applicant respectfully traverses the Examiner's statement at p. 8 of the Office Action to the effect that, "The instant examples employ EPO, not derivatives thereof." Applicants submit for the Examiner's consideration in this regard that Examples 3 and 4 in the present application do in fact disclose the use of an EPO derivative, namely Aranesp. The same derivative was used, in fact, in the experiments described in the paper by Bahlmann et al. (2004) discussed above. One having an ordinary level of skill in this field typically does not use natural erythropoietin (EPO) either when experimenting in this area or when engaging in a therapeutic treatment. Instead, such individuals tend to use derivatives of EPO such as Aranesp (i.e., Darbepoietin) which are well known to those of ordinary skill in this field, which have been approved by the relevant governmental authorities and which are clearly described in the present application. Applicants thus respectfully submit that in light of the remarks above they believe that the application as filed provides ample evidence that one of ordinary skill is sufficiently enabled to use EPO derivatives.

Applicants thus contend that the method of treating acute or chronic renal failure as recited in pending claims 54 and 57, i.e., involving administration of EPO or a derivative thereof in a low (subpolycythemic) dosage to human or animal patient exhibiting at least one condition from a), b) and c), is both novel and non-obvious in view of the present state of the art in this field. One skilled in this art would not consider a conventional mode of treatment utilizing a high dosage of EPO (or a derivative thereof - see the discussion above re: derivatives) since relatively high dosages of EPO are known to produce undesirable side effects, such as an elevation of the hematocrit, hypertonia, thrombosis and the potential to cause disease conditions, such as a stroke, particularly in patients exhibiting cardiovascular risk factors. Since the present group of patients, however, is characterized by the presence of cardiovascular risk factors and endorgan damages and is therefore particularly susceptible to such undesired effects, conventional EPO therapies are contra-indicated.

Furthermore, one having an ordinary level of skill in this field also would not be led by the prior art in this field, taken together with the common general knowledge of one working therein, to consider a treatment involving low doses of EPO (or a derivative) in patients exhibiting renal insufficiency - since these patients are still able to produce endogenous EPO.

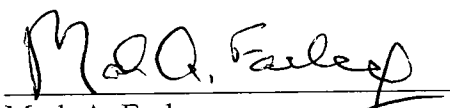
Those of ordinary skill in the art are, in fact, aware of a control mechanism that is initiated by such endogenously produced EPO. According to this mechanism, an elevation of the circulating pool of EPO causes a reduction in the amount of endogenous EPO produced by the kidney. The EPO clearance in such case is reciprocal to the amount of exogenous EPO administered. This means that the lower the amount of EPO that is added, the higher will be the EPO clearance. Taking this well-known control mechanism into account, the application of exogenous EPO would cause a corresponding reduction in the amount of endogenous EPO produced by a patient undergoing such treatment. The above, thus, would suggest to one having ordinary skill in the art not to treat the conditions recited in, e.g., claim 57 with low doses of EPO.

Surprisingly, however, applicants have shown that the method recited in the pending claims 54 and 57 is able to successfully treat patients suffering from acute or chronic renal failure exhibiting at least one of conditions a), b) and c) as recited in claim 54 with the administration of a subpolycythemic dosage of at least one of EPO or a derivative thereof constituting 1-90 IU EPO/kg of body weight per week.

In accordance with applicants' remarks as set forth above, taken in conjunction with the evidence provided in the accompanying declaration of Prof. Dr. Hermann Haller, the Examiner is respectfully requested to reconsider and withdraw the various rejections of applicants' claims as set forth in the present Office Action and to issue a Notice of Allowance for the pending claims presently under examination.

THIS CORRESPONDENCE IS BEING SUBMITTED ELECTRONICALLY THROUGH THE PATENT AND TRADEMARK OFFICE EFS FILING SYSTEM ON February 1, 2010.

Respectfully submitted,



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